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10/700,632	11/05/2003	Mary G. Hoffee	A-8427	8127

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SUGHRUE MION, PLLC  
2100 PENNSYLVANIA AVENUE, N.W.  
SUITE 800  
WASHINGTON, DC 20037

EXAMINER

BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/700,632

Applicant(s)

HOFFEE ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-71 is/are pending in the application.
- 4a) Of the above claim(s) 33-58 and 63-71 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 16 is/are allowed.
- 6) ☒ Claim(s) 1-15, 17-32 and 59-62 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 11/5/03; 2/1/05
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Exhibit A

### **DETAILED ACTION**

1. Claims 1-71 are pending

#### ***Election/Restrictions***

2. Applicant's election without traverse of Group I, claims 1-32 and 59-62 in the reply filed on 22 March 2006 is acknowledged. The examiner acknowledges applicant's request for rejoinder of the process claims that depend from or otherwise including all of the limitations of the allowable product claims. See MPEP 821.04.
3. Claims 33-58 and 63-71 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.
4. Claims 1-32 and 59-62 are under examination.

#### ***Specification***

5. The abstract of the disclosure is objected to because the abstract of the disclosure uses the legal phraseology "said antibodies" on lines 2-4.  
Correction is required. See MPEP § 608.01(b).
6. The disclosure is objected to because of the following informalities:
  - a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 33, paragraph [171]. Applicant's cooperation is requested in reviewing the entire disclosure for additional embedded hyperlinks and/or other form of browser-executable code that require correction. See MPEP § 608.01.

b. The specification discloses "5 ?" at pg. 33, last line, pg. 34, paragraphs [175] and [178] and discloses "derives from the mouse IgV? 8-27 germline" at pg. 41, paragraph [201]. It is unclear what the "?" is meant to represent. Clarification and/or correction is requested. Applicant's cooperation is requested in correcting any additional errors of which applicant may become aware in the specification.

c. Figure 8A and 8B show the cDNA sequence and deduced amino acid sequence of the light and heavy chain variable regions, respectively, however, the drawings only provide a single sequence identifier. "It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP 2422.02.

d. The use of the trademark Titertek® has been noted in this application (see pp. 39 and 40). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 59-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 59-60 are indefinite in the recitation of "improved antibody or epitope binding fragment thereof" because the claims do not state the function, which is to be achieved. The term "improved" is relative in nature, which renders the claims indefinite. The term "improved" is not defined by the claim; the specification does not provide a standard for ascertaining the direction, requisite degree or endpoint, and one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention. What functional attribute of the claimed antibody or antibody fragment is "improved"?

### ***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-14, 17-32 and 59-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibodies and epitope-binding fragments thereof that specifically bind CD33 and comprise the heavy chain CDRs of SEQ ID Nos:1-3 and the light chain CDRs of SEQ ID Nos:4-6 or comprises the heavy chain variable region of SEQ ID NO:7 and/or the light chain variable region of

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SEQ ID NO:8 or comprising the heavy chain variable region of SEQ ID NO:9 and/or the light chain variable region of SEQ ID NO:10 as well as conjugates thereof and compositions comprising said isolated anti-CD33 antibodies or epitope-binding fragments thereof, does not reasonably provide enablement for (i) isolated antibodies and epitope-binding fragments thereof comprising at least one CDR selected from SEQ ID Nos:1-6 or (ii) comprising all six CDRs (SEQ ID Nos:1-6) or comprising the heavy chain variable region of SEQ ID NO:7 or 9 or comprising the light chain variable region of SEQ ID NO:8 or 10 wherein the antibody does not bind CD33 or (iii) comprising a heavy chain variable region having at least 90% or 95% sequence identity to SEQ ID NO:7 or SEQ ID NO:9 or comprising a light chain variable region having at least 90% or 95% sequence identity to SEQ ID NO:8 or 10 wherein the antibodies do not bind CD33 or (iv) improved antibodies and epitope-binding fragments thereof comprising at least one mutation, deletion, insertion or addition wherein the antibodies bind CD33. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered proteins and antibodies where the relative level of skill of those in the art is deemed to be high.

The claims are drawn to isolated antibodies or epitope-binding fragments thereof comprising at least one CDR selected from SEQ ID Nos:1-6 and antibodies or epitope-binding fragments thereof comprising the heavy chain CDRs of SEQ ID Nos:1-3 and the light chain CDRs of SEQ ID Nos:4-6 wherein the antibody or epitope-binding fragments thereof do not bind CD33 (i.e., claim 2) and antibodies or epitope-binding fragments thereof comprising a heavy chain variable region having at least 90% sequence identity with the heavy chain variable region of SEQ ID NO:7 or 9, or comprising a light chain variable region having at least 90% sequence identity with the light chain variable region of SEQ ID NO:8 or 10, wherein the antibodies do not bind CD33 as well as conjugates and compositions comprising said antibodies or epitope-binding fragments thereof. Further, claims 59-62 are drawn to improved antibodies or epitope-binding fragments thereof comprising the heavy chain variable region of SEQ ID NO:7 and/or the light chain variable region of SEQ ID NO:8 or comprising the heavy chain variable region of SEQ ID NO:9 and/or the light chain variable region of SEQ ID NO:10 and having at least one mutation, deletion, insertion or addition into the sequence of said antibodies.

The specification discloses only antibodies that specifically bind CD33 and comprise all 6 CDRs (SEQ ID Nos:1-6) or comprise the heavy and light chain variable domains of SEQ ID Nos:7 and 8, respectively, (i.e., monoclonal antibody My9-6) (see Examples). The specification does not teach antibodies comprising at least one CDR

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selected from SEQ ID Nos:1-6 or comprising all six CDRs (SEQ ID Nos:1-6), or comprising a heavy and/or light chain that is at least 90-95% identical to SEQ ID Nos:7 and/or 8, respectively, or comprising a heavy and/or light chain that is at least 90-95% identical to SEQ ID Nos:9 and/or 10, respectively, wherein the antibody does not bind CD33; or improved antibodies comprising just any mutations, deletions or insertions and the antibodies bind CD33. There are no working examples of antibodies comprising at least one CDR selected from SEQ ID Nos:1-6, or comprising all six CDRs (SEQ ID Nos:1-6), or comprising a heavy and/or light chain that is at least 90-95% identical to SEQ ID Nos:7 and/or 8, respectively, or comprising a heavy and/or light chain that is at least 90-95% identical to SEQ ID Nos:9 and/or 10, respectively, wherein the antibody binds CD33; or improved antibodies comprising just any mutations, deletions or insertions and the antibodies bind CD33. Therefore, the teachings in the specification are extremely narrow relative to the broad scope of the claims at issue. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3<sup>rd</sup> Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each

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of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman P. M. (Research in Immunology, 145:33-36, 1994) teach that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). It is unlikely that proteins and modified variable domains which do not contain all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their correct spatial orientation have the requisite CD33 antigen-binding function. Further, it is unlikely that antibodies that comprising a heavy and/or light chain variable region(s) having an amino acid sequence that is 90-95% identical to SEQ ID Nos:7 and/or 8, respectively, or 90-95% identical to SEQ ID Nos:9 and/or 10 as defined by the claims, have the required CD33 binding function. For example, Patti et al (US

2005/0287164 A1) teach an antibody (monoclonal antibody 12-9) comprising a light chain that is 93% identical to SEQ ID NO:8 and the antibody binds the ClfA antigen of *S. aureus* (see pp. 12-13 and Examples 2 and the alignment attached to the back of this Office Action; Exhibit A). The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies comprising fewer than all six CDRs (SEQ ID Nos:1-6) that bind CD33 or an antibody comprising a heavy chain having an amino acid sequence that is at least 90-95% identical to SEQ ID NO:7 or SEQ ID NO:9 and binds CD33 or an antibody comprising a light chain having an amino acid sequence that is at least 90-95% identical to SEQ ID NO:8 or 10 and binds CD33. Although the specification at pages 7 and 17-18 discloses that improved antibodies may be readily produced by mutation, deletion or insertion within the variable regions, particularly the CDRs using methods such as oligonucleotide-mediated site-directed mutagenesis, cassette mutagenesis, error-prone PCR, DNA shuffling or mutator-strains of *E. coli*, the specification does not provide sufficient guidance or direction as to the general tolerance to modification and extent of such tolerance in the variable regions; the specific positions of the variable regions which can be predictably modified and which regions are critical for maintaining CD33 binding function. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al., Science, 233:747-753, 15 August 1986).

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed antibodies in a manner reasonably correlated with the scope of the claims, broadly including less than all six CDRs of

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mouse monoclonal antibody My9-6 (i.e., SEQ ID Nos:1-6), or comprising a heavy and/or light chain variable region(s) having an amino acid sequence that is 90-95% identical to SEQ ID Nos:7 and/or 8, respectively, or 90-95% identical to SEQ ID Nos:9 and/or 10, respectively, or improved antibodies comprising any number of amino acid substitutions, deletions or insertions in the variable regions of SEQ ID Nos:7 and/or 8 or SEQ ID Nos:9 and/or 10. Without such guidance, the changes which can be made in the protein's structure and still maintain antigen-binding function is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F. 2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Coleman P. M., Patti et al and Amit et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibodies comprising at least one CDR selected from SEQ ID Nos:1-6, or comprising all six CDRs (SEQ ID Nos:1-6), or comprising a heavy and/or light chain that are/is at least 90-95% identical to SEQ ID Nos:7 and/or 8, respectively, or comprising a heavy and/or light chain that are/is at least 90-95% identical to SEQ ID Nos:9 and/or 10, respectively, wherein the antibody does not bind CD33; or improved antibodies comprising just any mutations, deletions or insertions wherein the antibodies bind CD33 with a reasonable expectation of success, absent a specific and detailed description in applicant's

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specification of how to effectively practice the claimed antibodies and absent working examples providing evidence which is reasonably predictive that the claimed antibodies bind CD33, commensurate in scope with the claimed invention.

Amending claim 2 to recite "An isolated antibody or epitope-binding fragment thereof that specifically binds CD38..." would overcome this rejection as it pertains to claims 2, 5, 8, 11, 14, 18, 20, 22, 24, 26, 28, 30 and 32.

### ***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-8 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Weitzhandler et al (Journal of Pharmaceutical Sciences, 83(12):1670-1675, December 1994) as evidenced by the specification.

Claim 1-8 and 15 is drawn to an isolated antibody or epitope-binding fragment thereof comprising at least one CDR having an amino acid sequence selected from SEQ ID Nos:1-6 and having the ability to bind CD33, or comprising a heavy chain variable region comprising the CDRs of SEQ ID Nos:1-3 and a light chain variable regions comprising the CDRs of SEQ ID Nos:4-6, or comprising a heavy chain variable region at least 90% identical to SEQ ID NO:7 or comprising a light chain variable region

at least 90% identical to SEQ ID NO:8, or comprising the heavy and light chain variable regions of SEQ ID Nos:7 and 8 respectively, wherein the antibody specifically binds CD33.

Weitzhandler et al teach murine monoclonal antibody My9-6 (see entire document, particularly pg. 1670, 2<sup>nd</sup>. Col., which is identical to the claimed murine monoclonal antibody My9-6 comprising the heavy and light chain variable regions of SEQ ID Nos:7 and 8, respectively, inclusive to the CDRs of SEQ ID Nos:1-6 as evidenced by the specification (see Figs 8A and 8B). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Accordingly, murine monoclonal antibody My9-6 taught by Weitzhandler et al necessarily comprises the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of SEQ ID NO:8 and binds CD33.

Thus, Weitzhandler et al anticipate the claims as evidenced by the specification.

13. Claims 1-8, 15 and 17-28 are rejected under 35 U.S.C. 102(b) as being anticipated by R & D Focus Drug News, 12 November 2001, as evidenced by the specification.

Claims 1-8 and 15 have been described supra.

Claims 17-28 further limit the claimed isolated antibody or epitope-binding fragment thereof of claims 1 and 2 by reciting that the antibody is linked to a drug or prodrug (immunoconjugate), or present in a composition also comprising a drug or prodrug, and wherein the antibody or immunoconjugate is present in a pharmaceutical composition comprising a pharmaceutically acceptable agent.

R & D Focus Drug News teach the anti-CD33 murine monoclonal antibody My9-6 linked to the maytansinoid drug DM1 (see entire document), wherein monoclonal antibody My9-6 is identical to the claimed murine monoclonal antibody My9-6 comprising the heavy and light chain variable regions of SEQ ID Nos:7 and 8, respectively, inclusive to the CDRs of SEQ ID Nos:1-6 as evidence by the specification (see Figs 8A and 8B and Example 4). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Accordingly, murine monoclonal antibody My9-6 taught by R & D Focus Drug News necessarily comprises the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of SEQ ID NO:8 and binds CD33. Further, given that that My9-6-DM1 immunoconjugate was shown to eliminate human tumor xenografts in mice in preclinical studies, one of ordinary skill in the art would readily envisage that the administered My9-6-DM1 immunoconjugate was necessarily present in composition or pharmaceutical composition comprising a pharmaceutically acceptable agent.

Thus, R & D Focus Drug News anticipate the claims as evidenced by the specification.

14. Claims 1-8, 15 and 17-28 are rejected under 35 U.S.C. 102(b) as being anticipated by CML NewsBytes, 10/24/2001, ([www.cmlsupport.com/cmlnewsbytesarchives2.htm](http://www.cmlsupport.com/cmlnewsbytesarchives2.htm)), as evidenced by the specification.

Claims 1-8, 15 and 17-28 have been described supra.

CML NewsBytes teach murine monoclonal antibody My9-6 linked to the maytansinoid drug DM1 (see entire document), wherein monoclonal antibody My9-6 is identical to the claimed murine monoclonal antibody My9-6 comprising the heavy and light chain variable regions of SEQ ID Nos:7 and 8, respectively, inclusive to the CDRs of SEQ ID Nos:1-6 as evidence by the specification (see Figs 8A and 8B and Example 4). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Accordingly, murine monoclonal antibody My9-6 taught by CML NewsBytes necessarily comprises the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of SEQ ID NO:8 and binds CD33. Further, given that that My9-6-DM1 immunoconjugate was shown to eliminate human tumors in mice, one of ordinary skill in the art would readily envisage that the administered My9-6-DM1 immunoconjugate was necessarily present in a composition or pharmaceutical

composition comprising a pharmaceutically acceptable agent. In addition, CML NewsBytes states that the drug My9-6-DM1 was to be evaluated and developed for human use. See *SmithKline Beecham Corp. v. Apotex Corp.*, 365 F.3d 1306 (Fed. Cir. 2004).

Thus, CML NewsBytes anticipates the claims as evidenced by the specification.

15. Claims 1-8, 15 and 17-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Lutz et al (Proceedings of the American Association for cancer research Annual Meeting, Vol. 43, p. 912, March 2002) or Goldmacher et al (Proceedings of the American Association for cancer research Annual Meeting, Vol. 43, p. 254, March 2002), as evidenced by the specification.

Lutz et al or Goldmacher et al teach murine monoclonal antibody My9-6 linked to the maytansinoid drug DM1 (see entire document), wherein monoclonal antibody My9-6 is identical to the claimed murine monoclonal antibody My9-6 comprising the heavy and light chain variable regions of SEQ ID Nos:7 and 8, respectively, inclusive to the CDRs of SEQ ID Nos:1-6 as evidence by the specification (see Figs 8A and 8B and Example 4). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Accordingly, murine monoclonal antibody My9-6 taught by Lutz et al or Goldmacher et al necessarily comprises the heavy chain variable region of

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SEQ ID NO:7 and the light chain variable region of SEQ ID NO:8 and binds CD33.

Further, given that that My9-6-DM1 immunoconjugate was shown to eliminate human tumors in mice, one of ordinary skill in the art would readily envisage that the administered My9-6-DM1 immunoconjugate was necessarily present in a composition or pharmaceutical composition comprising a pharmaceutically acceptable agent, particularly in view of the intravenous administration of Lutz et al.

Thus, Lutz et al or Golmacher et al anticipate the claims as evidenced by the specification.

### ***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 17-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg et al (U.S. Patent 6,759,045 B2, 8/8/2000) in view of R & D Focus Drug News, 12 November 2001, as evidenced by the specification.

The claims are being interpreted as drawn to the murine monoclonal antibody My9-6 comprising the heavy chain CDRs of SEQ ID Nos:1-3 and the light chain CDRs of SEQ ID Nos:4-6, wherein the My9-6 antibody is linked to a drug or prodrug as recited in claims 19-20 or wherein said My9-6 antibody or immunoconjugate thereof is present in a composition or pharmaceutical composition comprising a pharmaceutically acceptable agent as well as a diagnostic reagent comprising the My-9-6 antibody that is labeled with a biotin label, an enzyme, a radio-label, a fluorophore, a chromophore, an imaging agent or a metal ion.

Goldenberg et al teach anti-CD33 antibodies and immunoconjugates thereof for the treatment of leukemia, wherein the immunoconjugates comprise a drug, including calicheamicin or is labeled with a fluorescent or chromogenic agent for detection as well

as pharmaceutical compositions comprising the anti-CD33 antibodies or immunoconjugates thereof and a pharmaceutically acceptable carrier (see entire document, particularly columns 13-15 and 17). Goldenberg et al do not specifically teach presently claimed antibody or conjugates thereof or compositions comprising such. These deficiencies are made up for in the teachings of R & D Focus Drug News.

R & D Focus Drug News has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated the anti-CD33 My9-6 antibody as taught by R & D Focus Drug News with the various chemotherapeutic drugs (i.e., calicheamicin) or detectable labels of Goldenberg et al as well as produce pharmaceutical compositions comprising the My9-6 antibody or conjugates thereof and a pharmaceutically acceptable carrier for therapeutic benefit in leukemia patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have to have conjugated the anti-CD33 My9-6 antibody as taught by R & D Focus Drug News with the various chemotherapeutic drugs (i.e., calicheamicin) or detectable labels of Goldenberg et al as well as produce pharmaceutical compositions comprising the My9-6 antibody or conjugates thereof and a pharmaceutically acceptable carrier for therapeutic benefit in leukemia patients because Goldenberg et al teach anti-CD33 antibodies and immunoconjugates thereof for the treatment of leukemia, wherein the immunoconjugates comprise a drug, including calicheamicin or is labeled with a fluorescent or chromogenic agent for detection as well as pharmaceutical compositions

comprising the anti-CD33 antibodies or immunoconjugates thereof and a pharmaceutically acceptable carrier and R & D Focus Drug News teach the anti-CD33 murine monoclonal antibody My9-6 linked to the maytansinoid drug DM1 that effectively inhibited human tumor xenografts in mice and the My9-6 antibody is identical to the claimed murine monoclonal antibody My9-6 and necessarily comprises the heavy and light chain variable regions of SEQ ID Nos:7 and 8, respectively, inclusive to the CDRs of SEQ ID Nos:1-6, as evidenced by the specification. Therefore, given the success of the anti-CD33 My9-6 antibody in the treatment of tumor xenografts in mice, one of ordinary skill in the art would have been motivated to conjugate the My9-6 antibody to other suitable chemotherapeutic agents, which were known to those of skill in the art (see col. 14, lines 44-55) or conjugate the My9-6 antibody to a detectable label for diagnosis and administer the My-9-6 antibody or conjugates thereof in a pharmaceutically acceptable carrier in leukemia patients. Thus, there would be advantages to conjugating the My9-6 antibody to the various therapeutic and diagnostic agents and the inclusion of a pharmaceutically acceptable carrier facilitates administration in leukemia patients. Thus, it would have been *prima facie* obvious to one skilled in the art to have conjugated the anti-CD33 My9-6 antibody with various chemotherapeutic drugs (i.e., calicheamicin) or detectable labels as well as produce pharmaceutical compositions comprising the My9-6 antibody or conjugates thereof and a pharmaceutically acceptable carrier for therapeutic benefit in leukemia patients in view of Goldenberg et al and R & D Focus Drug News.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Conclusion***

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Zhao et al. American Chemical Society 224<sup>th</sup> National Meeting, August 18-22, 2002.

19. Claim 16 is free of the prior art. The prior art does not teach or fairly suggest a humanized anti-CD33 antibody comprising the heavy and light chain variable regions specified in the claim.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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you have questions on access to the Private PAIR system, contact the Electronic  
Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,  
David J. Blanchard  
571-272-0827

A handwritten signature in black ink, appearing to read "David Blanchard", written in a cursive style.

# Exhibit A

RESULT 1  
US-11-136-559-10  
; Sequence 10, Application US/11136559  
; Publication No. US20050287164A1  
; GENERAL INFORMATION:  
; APPLICANT: PATTI, Joseph M  
; APPLICANT: HUTCHINS, Jeff T  
; APPLICANT: DOMANSKI, Paul  
; APPLICANT: PATEL, Pratiksha  
; APPLICANT: HALL, Andrea  
; TITLE OF INVENTION: MONOCLONAL ANTIBODIES TO THE CLFA PROTEIN . . .  
; FILE REFERENCE: P07069US04/BAS  
; CURRENT APPLICATION NUMBER: US/11/136,559  
; CURRENT FILING DATE: 2005-05-25  
; PRIOR APPLICATION NUMBER: US/10/056,052  
; PRIOR FILING DATE: 2002-01-18  
; PRIOR APPLICATION NUMBER: 60/308,116  
; PRIOR FILING DATE: 2001-07-30  
; PRIOR APPLICATION NUMBER: 60/298,413  
; PRIOR FILING DATE: 2001-06-18  
; PRIOR APPLICATION NUMBER: 60/274,611  
; PRIOR FILING DATE: 2001-03-12  
; PRIOR APPLICATION NUMBER: 60/264,072  
; PRIOR FILING DATE: 2001-01-26  
; NUMBER OF SEQ ID NOS: 29  
; SOFTWARE: PatentIn version 3.1  
; SEQ ID NO 10  
; LENGTH: 112  
; TYPE: PRT  
; ORGANISM: Staphylococcus aureus  
US-11-136-559-10

Query Match 93.6%; Score 544; DB 11; Length 112;  
Best Local Similarity 92.9%; Pred. No. 2.5e-33;  
Matches 104; Conservative 5; Mismatches 3; Indels 0; Gaps 0;

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Db      1 NIMMTQSPSSLAVSAGEKVTMSCKSSQSVLYSSNQKNYLAWYQQKPGQSPKLLIYWASTR 60

QY      61 ESGVPDRFTGSGSGTDFLTITSSVQSEDLAIYYCHQYLSSTRTFGGGTKLEIK 112
      |||:|||||:|||||:|||||:|||||:|||||:|||||:|||||:|||||:
Db      61 ESGVPDRFTGSGSGTDFLTITSSVQAE DLAVYYCHQYLSSTRTFGGGTKLEIK 112
```